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EDITORIAL

Lowering vascular calcification burden in chronic kidney disease: Is it possible?

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Abstract

High prevalence of atherosclerosis and arterial calcification in chronic kidney disease is far beyond the explanation by common cardiovascular risk factors such as aging diabetes, hypertension and dyslipidemia. The magnitude of coronary artery calcification is independently and inversely associated with renal function. In addition to cardiovascular risk factors, other chronic kidney disease-related risks such as phosphate retention, excess of calcium and prolonged dialysis vintage also contribute to the development of vascular calcification. Strategies to lower vascular calcification burden in chronic kidney disease population should include minimizing chronic kidney disease and atherosclerotic risk factors. Current therapies available are non-calcium containing phosphate binders, low dose active vitamin D and calcimimetic agent. The role of bisphosphonates in vascular calcification in chronic kidney disease population remains unclear. Preliminary data on sodium thiosulfate are promising, however, larger studies on efficacy and patient outcomes are necessary. Several large randomized controlled trials have confirmed the lack of benefit of statin in attenuating the progression of vascular calcification.

Key words: Coronary calcification; Coronary artery calcification; Renal failure; Phosphate; Vitamin D

Core tip: High prevalence of atherosclerosis and arterial calcification in chronic kidney disease is far beyond the explanation by common cardiovascular risk factors. Phosphate retention, excess of calcium and prolonged dialysis vintage also contribute to the development of vascular calcification. Current therapies available include non-calcium containing phosphate binders, low dose active vitamin D and calcimimetic agent. The role of bisphosphonates is unclear. Preliminary data on sodium thiosulfate are promising. Several randomized studies revealed the lack of benefit of statin in lowering vascular calcification.

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INTRODUCTION

The leading cause of mortality in chronic kidney disease (CKD) population is cardiovascular disease[1]. Traditional cardiovascular risk factors including aging, diabetes, hypertension and dyslipidemia are common among CKD patients. However the high prevalence of atherosclerosis and arterial calcification in CKD is far beyond the explanation by common cardiovascular risk factors[2,3]. Previous studies have demonstrated increasing prevalence of vascular calcification starting from early stages of CKD toward the end-stage renal disease. In a large cohort of CKD patients, the magnitude of coronary artery calcification (CAC) was independently and inversely associated

with the estimated glomerular filtration rate (eGFR)[4]. In addition to common cardiovascular risk factors, other CKD-related risks such as phosphate retention, excess of calcium and prolonged dialysis vintage also contribute to the development of vascular calcification[3,5].

Vascular calcification is a complex cell-mediated process involving the transformation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells. The transformed VSMCs subsequently produce several bone matrix proteins in preparation for mineral crystals deposition, a process resembling biomineralization[6]. In addition to the release of matrix vesicles required for the nucleation of mineral crystals, apoptotic bodies derived from dying VSMCs which are able to concentrate calcium and phosphate in the same fashion as matrix vesicles are also present[7]. Several factors present in CKD milieu such as high phosphate and calcium environment, high doses of active vitamin D and klotho deficiency can promote VSMCs transformation and vascular calcification[8-10]. Reduced concentrations or abnormal metabolism of naturally occurring calcification inhibitors including fetuin A, inorganic pyrophosphate, matrix gla protein and osteoprotegerin also contribute to the severity of vascular calcification in CKD[11-14].

Kidney transplantation offers a mean to restore kidney function and mineral metabolism at the same time. Studies that followed kidney transplant recipients for 1-2 years revealed stabilization or progression of vascular calcification but at a much slower rate compared to patients who remained on dialysis[15-17]. Following kidney transplant recipients further for 2.5-4.0 years revealed a progression of CAC at a rate of 11% per year[18,19]. In addition to the severity of baseline calcification, the presence of dyslipidemia appeared to be a common factor associated with the progression of vascular calcification in long-term. These data suggested that vascular calcification, once occurred, is unlikely to reverse. Removal of CKD-related risk factors through kidney transplantation may attenuate the rate of progression compared to those who remained on dialysis. However, progression will eventually take place due to the presence of common risk factors such as aging, diabetes, hypertension and dyslipidemia.

Strategies to lower vascular calcification burden in CKD population should include minimizing CKD risk factors, for example, phosphate retention, excess of calcium, high doses of vitamin D treatment and modifying other atherosclerotic risks. The following review focuses on therapies that may have favorable impact on vascular calcification and/or patient outcomes in CKD population.

NON-CALCIUM CONTAINING PHOSPHATE BINDERS

Several studies have demonstrated the relationship between the amount of calcium intake derived from calcium-containing phosphate binders and the severity of vascular calcification[3,5]. Newer non-calcium containing phosphate binders including sevelamer and lanthanum may have favorable impact on vascular calcification. In three randomized controlled trials in hemodialysis patients, sevelamer and lanthanum attenuated the progression of CAC compared to calcium-containing phosphate binders[20-22]. The mortality benefits of both drugs were observed only in a subgroup of patients older than 65 years of age[23,24]. In a small randomized controlled trial in incident hemodialysis patients, sevelamer was associated with a survival benefit compared to calcium[25]. In early stages of CKD, serum phosphate remains within the normal range in most patients; however, phosphate retention is already present as evidenced by elevated parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) levels starting as early as CKD stages 2-3[26,27]. The rise in PTH results in an increased expression of sodium-phosphate co-transporter in proximal tubules augmenting renal phosphate excretion. FGF-23, in the presence of its obligatory co-receptor klotho, upregulates sodium phosphate co-transporter and suppresses 1,25-dihydroxyvitamin D synthesis[28]. High normal serum phosphate as well as elevated PTH and FGF-23 levels have been shown to predict mortality in non-dialysis dependent CKD population[26,29]. Attempts have been made to study the benefit of phosphate binders in early stages of CKD. In a randomized controlled trial comparing sevelamer to calcium in non-dialysis CKD stages 3-5 patients, the use of sevelamer was associated with a better survival[30]. Most patients in this study did not have hyperphosphatemia and phosphate binders were mostly given at a fixed dosage aiming at reducing renal phosphate excretion. However, subsequent small randomized study in CKD stages 3b-4 patients comparing calcium, sevelamer and lanthanum versus placebo revealed an increase in arterial calcification in all groups of patients that received phosphate binders but the degree was highest in the calcium group[31]. It was speculated that phosphate binders could result in an increased availability of free calcium in the intestine. There were several flaws in the study and results must be interpreted with cautions[32]. Another small sized randomized study in CKD stages 3b-4 patients comparing rosuvastatin, sevelamer and no drug also revealed an increase in CAC score in all groups[33]. It is obvious that a larger study is needed to clarify the beneficial or harmful effects of phosphate binders in early stages of CKD.

ACTIVE VITAMIN D

Active vitamin D (calitriol, alfacalcidol, doxercalciferol, paricalcitol) in high doses are commonly prescribed to lower PTH in CKD patients. Active vitamin D drugs that are closely related to the parent compound (calcitriol) such as alfacalcidol and doxercalciferol, in addition to suppressing PTH secretion, can also enhance intestinal calcium and phosphate absorption resulting in hypercalcemia and hyperphosphatemia. A newer vitamin D analog, paricalcitol, is supposed to act preferentially at parathyroid glands with less calcemic and phosphatemic effect in the gastrointestinal tract[34]. In an experimental study in rodents, calcitriol, alfacalcidol and doxercalciferol poten-

tiated the development of vascular calcification whereas paricalcitol did not[35]. Subsequent experimental study using different doses of active vitamin D demonstrated that both calcitriol and paricalcitol in high doses stimulated the development of vascular calcification whereas lower doses were protective[9]. Recent study in hemodialysis patients also revealed similar incidence of hypercalcemia and hyperphosphatemia in patients who received alfacalcidol and paricalcitol[36]. In a 2-year observational study in chronic hemodialysis patients, those who received higher prescribed dose of alfacalcidol experienced a slower rate of progression of aortic arch calcification[37]. These data suggested that lower doses of active vitamin D drugs may have protective effect on vascular calcification. In a uremic mouse model of extensive arterial calcification, low doses of calcitriol and paricalcitol were associated with half of the aortic calcification compared to no therapy. In this study, active vitamin D treatment resulted in an increase in soluble alpha-klotho, a heightened renal phosphate excretion and lower serum phosphate[38]. Klotho deficiency occurs early in the course of CKD and introduction of klotho gene into CKD mice was able to rescue the vascular calcification phenotype[10]. These data suggested that the protective effect of low dose vitamin D on vascular calcification may be related to the restoration of klotho expression. The impact of active vitamin D on survival were described in observational and retrospective studies mostly in hemodialysis patients[39-42]. Survival benefit was more pronounced in the groups of patients that received lower doses and was observed at all PTH levels. At the time of this review, there is no published randomized study evaluating the effect of active vitamin D treatment on survival in CKD population.

CALCIMIMETIC

Calcimimetic drug is an allosteric activator of calcium-sensing receptor that has the ability of suppress PTH secretion without increasing serum calcium. Cinacalcet, the only drug in this class, is used successfully in conjunction with active vitamin D and phosphate binder in the treatment of hyperparathyroidism in dialysis patients[43]. In an experimental study in nephrectomized rats, unlike calcitriol, the PTH lowering effect of cinacalcet was not associated with a development of vascular calcification[44,45]. In a randomized controlled study in 360 hemodialysis patients, adding cinacalcet to low dose active vitamin D attenuated the progression of vascular and aortic valve calcification[46,47]. However, a large randomized controlled trial in 3883 hemodialysis patients with a 2-year follow-up did not show survival or cardiovascular benefits associated with cinacalcet use[48].

MAGNESIUM AND COMBINED MAGNESIUM-CALCIUM PHOSPHATE BINDER

Intracellular and extracellular magnesium are important in preventing oxidative stress and inflammation. Decreased magnesium is associated with impaired endothelial function, vasospasm and atherogenesis[49]. In hemodialysis and peritoneal dialysis patients, lower serum magnesium but still within the normal range was associated with an increased severity of vascular calcification[50,51]. *In vitro* studies have demonstrated the protective effect of increasing magnesium concentration on vascular smooth muscle cell calcification through an upregulation of anti-calcification proteins including matrix gla protein and osteopontin[52-54]. The combined magnesium-calcium phosphate binder (calcium acetate 435 mg/magnesium carbonate 235 mg) available in Europe has similar efficacy to sevelamer in reducing serum phosphate and without the side effect of increasing serum ionized calcium. In a 24-wk follow-up study in 204 hemodialysis patients, a slight but significant increase in serum magnesium was observed in those who received the combined magnesium carbonate phosphate binder. All patients were dialyzed against 0.5 mmol/L magnesium dialysate and experienced no serious adverse events[55]. In a small observational study in hemodialysis patients, CAC score was unchanged after 18 mo of being on the combined magnesium phosphate binder[56].

BISPHOSPHONATE

Bisphosphonates are analogs of inorganic pyrophosphate. In addition to suppression of osteoclast and bone resorption, bisphosphonates can also inhibit calcium and phosphate crystals deposition. Bisphosphonate has been used successfully in the treatment of calcific uremic arteriolopathy (CUA)[57]. In two observational studies in hemodialysis patients, intermittent oral or parenteral etidronate for 6 mo delayed the progression of CAC and aortic calcification[58,59]. In a small randomized controlled study in 46 CKD stages 3-4 patients, there was no difference in the rate of progression of aortic calcification in patients who were randomized to alendronate 70 mg weekly compared to placebo after 18 mo of follow-up[60]. Analysis of vascular and valvular calcification in 3710 women in MESA (Multi-Ethnic Study of Atherosclerosis) cohort revealed a lower prevalence of cardiovascular calcification associated with the use of bisphosphonate in older women ($\geqslant$ 65 years), whereas calcification was more prevalent in the younger ones ($\leqslant$ 65 years)[61]. There are also concerns regarding worsening adynamic bone disease with the use of bisphosphonates in CKD population. The recent Kidney Disease: Improving Global Outcomes recommendations suggested not to prescribe bisphosphonate in patients with eGFR less than 30 mL/min per 1.73 m^2[62].

SODIUM THIOSULFATE

Sodium thiosulfate (STS) is a reducing agent, an antioxidant and a chelator. STS is used as an antidote in cyanide poisoning. STS can also chelate calcium in precipitated minerals giving rise to calcium thiosulfate, which is sever-

al folds more soluble than calcium phosphate or calcium oxalate. STS has been used successfully in conditions with increased calcification burden including nephrolithiasis, CUA and soft tissue calcification[63-65]. A large observational study in 172 hemodialysis patients with CUA who received intravenous STS therapy revealed clinical improvement in most patients[66]. Oral bioavailability of STS is low; therefore, STS should only be given by parenteral route. Intravenous and intraperitoneal administration of STS in hemodialysis and peritoneal dialysis patients are well tolerated and adverse events are mild[66-68]. STS is readily cleared by dialysis[69]. In two preliminary studies in hemodialysis patients, STS was able to delay the progression of CAC after 4-5 mo of twice weekly intravenous administration but with a decline of hip bone mineral density in one study[67,70]. Larger studies are required to confirm the efficacy of STS on vascular calcification.

INTERMITTENT PTH

The relationship between low bone mass and the severity of vascular calcification has long been documented in general population[71]. Decreased bone formation and/or augmented bone resorption may result in an increase in calcium and phosphate availability potentiating the development of vascular calcification. The N-terminal fragment of PTH (1-34), when given intermittently, is osteoanabolic. Daily injection of human PTH (1-34) or teriparatide has been used effectively to increase bone formation in general population with osteoporosis. In a LDLR-/- mouse model with obesity, diabetes, dyslipidemia and vascular calcification, intermittent PTH (1-34) administration suppressed vascular calcification by downregulating osteogenic pathway in the arterial wall[72]. In a small observational study in 7 hemodialysis patients with adynamic bone disease (PTH = 22 pg/mL), a 6 mo course of teriparatide raised the BMD of lumbar spine and femoral neck while attenuating the progression of CAC[73].

Therapies aim at lowering risk factors associated with atherosclerosis such as statin has been subjected to clinical trials. Several large randomized controlled studies in general population revealed no benefits of intensive statin therapies on CAC progression[74-76].

In conclusion, current therapies available for vascular calcification in CKD include non-calcium containing phosphate binders, low dose active vitamin D and calcimimetic agent. The role of bisphosphonates in vascular calcification in CKD population remains unclear. Preliminary data on sodium thiosulfate is promising. However, larger studies on efficacy and patient outcomes are necessary. Several large randomized controlled trials have confirmed the lack of benefit of statin in attenuating the progression of vascular calcification.

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